Group 4: fibrosis judged to be already present—27 patients, first seen at an average interval of five and a half years from the apparent onset.

In group 1 the good prognosis reported previously was confirmed. After five years 27 patients (84%) had clear chest radiographs and 31 (97%) were free from symptoms. Only one patient had appreciable disability.

In group 2 23 patients (53%) had attained resolution of all radiographic shadows; another 2 (5%) had some residual radiographic abnormality but no symptoms; and 11 (28%) had radiographic abnormalities with only mild symptoms. Only 3 (7.5%) had moderately severe symptoms interfering with normal life. One had died of an unrelated cause.

In group 3 16 patients (43%) had attained radiographic resolution; 6 (16%) had some residual changes with no disability; 8 (22%) had residual changes with slight disability; and 6 (16%) had moderate disability. One had died of an unrelated cause.

In group 4 six patients died of pulmonary fibrosis due to sarcoidosis in the sixth to twenty-fifth year of the disease. One died of an unrelated cause. Of the remaining 20, 10 remained unchanged, 7 showed some improvement, and 3 became worse during the five years' observation.

Only a minority of the patients were treated with corticosteroids. Reasons are given for the conclusion that this measure did not affect the principal criterion of prognosis adopted—the attainment and maintenance under prolonged observation of a normal chest radiograph.

An onset with erythema nodosum was found to be associated highly significantly with a good prognosis.

Sarcoid skin lesions were significantly associated with a poor prognosis for the lung changes.

Sarcoidosis of the eye, generalized lymphadenopathy, and palpability (as opposed to gross enlargement) of the spleen did not seem to affect the prognosis of the lung changes.

Twelve pregnancies occurred in 10 women during the observation period. During four of these pregnancies shadows in the lungs cleared, only to return after delivery. Apart from this, the pregnancies appeared to have no effect on the course of sarcoidosis.

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The Royal Scottish Nursing Home in Edinburgh, which was taken over by the Nuffield Nursing Homes Trust in May last year, has now been officially reopened. It has been completely modernized and can now accommodate 48 patients. (*Scotsman*, September 29.)

THE BIRMINGHAM ORAL CONTRACEPTIVE TRIAL

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In March, 1960, the Birmingham Family Planning Association embarked on its first oral contraceptive trial. Its objects were twofold. First, in view of the existing widespread dissatisfaction with conventional techniques of birth control, it seemed desirable to assess the efficacy and acceptability of the method among British women. Second, while the ability of relatively large doses of oral contraceptives to control fertility had been adequately established (Pincus *et al.*, 1958, 1960), there was next to no information about the effect of lower doses with regard to both the suppression of ovulation and the incidence and severity of side-effects. With these aims in mind—and that of reducing the substantial cost of the larger dosage—the Executive Council of the Birmingham F.P.A. decided to conduct a trial on a reasonably large scale and under carefully controlled conditions laid down and supervised by a specially enlisted Medical Advisory Committee.

Messrs. G. D. Searle and Co. Ltd. agreed to support the trial both financially and by supplying adequate quantities of the test material (norethynodrel) to the Medical Advisory Committee.

The following account reports findings obtained with the 2.5-mg. strength of tablet (1 OC trial). As soon as it became apparent that this dosage provided insufficient conception control, the strength of tablets taken by volunteers was increased to 5 mg. a day. Those who had not conceived up to this moment and wished to continue, as well as new volunteers not previously employed, were enlisted in further trials (2 OC and 3 OC), and to date no failures have occurred among women participating in either of these two trials in the prescribed manner. Where possible, provisional information about the results with the 5-mg. tablet is included, but a full report must be deferred until the 2 OC and 3 OC trials have been completed.

Subjects and Experimental Procedures

Selection of Participants

These were chosen from the large number of women who had responded to the appeal for volunteers. They had to satisfy the following criteria:

(*a*) *Age* under 36 years at the time of beginning the trial.

(*b*) *Proved fertility*: possession of at least one living child of the present marriage; not more abortions than children.

(*c*) *Body weight* not exceeding 11 stone (70 kg.).

(*d*) *Menstrual cycles* not varying beyond the range of 23–32 days within the past year.

(*e*) *General health* (of both volunteer and husband) must be satisfactory.

(*f*) *Coitus*: average frequency not less than once weekly.

(*g*) *Clinical examination*: normal findings at abdominal and pelvic examination.

(*h*) *Residence* within easy access of Birmingham.

All volunteers conforming to the above criteria were asked to agree to remain in the trial for a minimum of six months, and during that time to use no other form of contraceptive. It was explained to them that the efficacy of the method could not be guaranteed, and all accepted the possibility of another pregnancy in the event of failure of the tablets. In addition, each woman was required to return a consent form signed by both her husband and herself; her medical practitioner was also informed.

It had been the Committee's intention to enlist not fewer than 100 participants. Only 52 volunteers fulfilling the above criteria had been enlisted before it was decided to close the first trial. Of these 52, one was discovered to be pregnant and three others withdrew before the start of the trial, thus leaving 48 (Table I). The following report is based on the findings obtained in these 48 women.

Composition and Dosage of Test Substance

The compound selected was norethynodrel (17α-ethinyl-5(10)-oestraenolone) 2.5 mg. with 0.05 mg. of the highly potent oestrogen, ethinyloestradiol-3-methyl ether (EO-3-ME). Subsequent chemical analysis carried out in the manufacturers' laboratories in the United States revealed, however, that the oestrogen content of the batch of tablets actually used in the trial was less, and amounted to 0.036 mg.; the concentration of norethynodrel proved to be approximately correct (2.3 mg.). The tablets supplied during the 2 OC trial contained 5 mg. of norethynodrel and 0.075 mg. of EO-3-ME.

Administration of Tablets and General Procedure

Although similar in outline to other clinical trials—for example, Pincus *et al.* (1960) and Mears (1961)—there were certain differences in procedure. Counting the first day of bleeding as day 1, one tablet was taken nightly from day 5 to 24 of the cycle. Then followed an interval of eight clear days until the start of the next course of tablets, whether a period had occurred (Fig. 1*a*) or not (Fig. 1*b*). Later this interval was reduced to six days. If breakthrough bleeding occurred—here defined as bleeding before the end of a course of tablets—medication was to be stopped and a new course begun on the fifth day of the (breakthrough) bleeding (see Fig. 1*c*).

All participants were requested to maintain a regular and faithful daily record of tablet-taking, incidence of menstruation (including "spotting"), sexual intercourse, and side-effects on specially provided diary cards (Fig. 2). These were given to them together with bottles containing 20 tablets—enough for one full course—of norethynodrel, and had to be returned after the

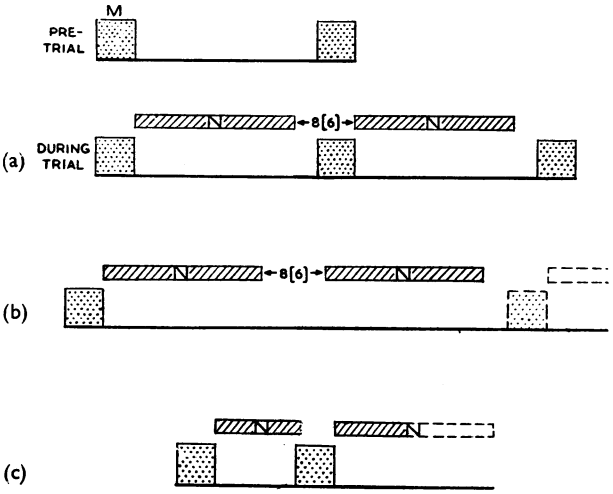

FIG. 1.—Diagrammatic representation of experimental procedure. M, menstruation; N, course of norethynodrel. (*a*) Normal sequence of cycles (above, pre-trial; below, during trial). (*b*) Amenorrhoea. (*c*) Breakthrough bleeding.

completion of either one or two courses to the F.P.A. clinic before new supplies were issued.

The women were also advised to disregard minor ailments (such as a cold), but in the event of more serious illness to consult either the medical officer in charge of the trial or their own practitioners.

All volunteers were interviewed and, if necessary, examined when reporting at the end of every second course of medication. In the event of amenorrhoea (exceeding, initially, six weeks), they were asked to collect specimens of urine and dispatch them to the clinic for (Aschheim–Zondek) pregnancy tests. If the test was negative but amenorrhoea persisted, repeat tests were carried out at intervals of a few weeks until the diagnosis was established.

The first volunteers started on the medication—and with it the trial as a whole began—in June, 1960. When, approximately three months later, it became evident that several conceptions had occurred, all women were asked to report to the clinic without delay, where the position was explained to them. They were

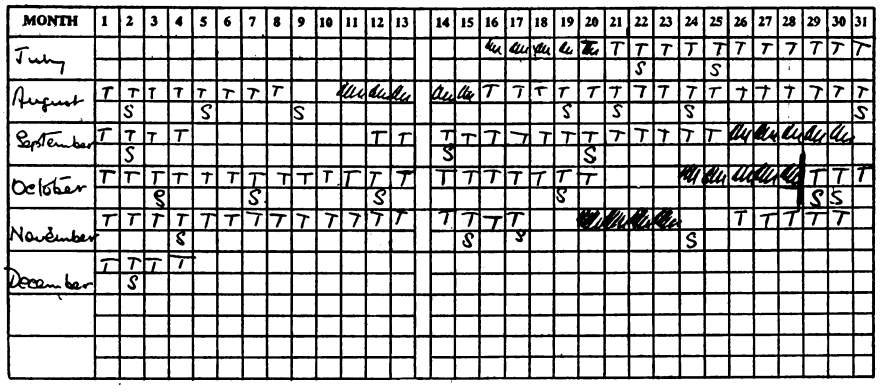

FIG. 2.—Photocopy of volunteer's diary card during trial. T, tablets; ▓, bleeding; S, sexual intercourse; ▮, transfer to 2 OC trial (October 29, 1960).

then asked to complete the current cycle and to start a new course (on the fifth day of bleeding, as usual) with a fresh supply of 5-mg. tablets issued to them. If menstruation was delayed, they were to use conventional methods of contraception before beginning to take the new type of tablet.

Generally speaking, all these arrangements worked well. Neither the patients' trust nor contact with them was lost, and most of those who had not conceived by the time of the changeover to the 5-mg. tablets continued with the trial.

Although it had been hoped originally to examine cervical smears and obtain endometrial biopsies during the first trial, neither was in fact possible. The results of such examinations carried out in the course of the second and third trials (2 OC and 3 OC) are to be reported in due course.

Every effort was made to follow up the course of pregnancy and delivery of women who conceived, in order to ascertain, so far as was possible, the length of gestation, likely date of conception, and the condition of the newborn. All deliveries have now taken place.

I. General Results

A total of 48 women embarked on the trial, of whom 14 conceived (see section II below, and Table I).

TABLE I.—*Distribution of Cases*

Originally enrolled	52
Removed before start of trial	4*
Included in first trial (1 OC)	48
Conceived	14
Did not conceive while on trial	34

* Voluntary withdrawal, 3; pregnant before trial, 1.

The remaining 34 subjects have been transferred to the second trial (2 OC; 5-mg. tablets), and while continuing on it none of them had conceived up to the time of writing—a period extending in some cases to almost a year.

The observations on menstrual periodicity and side-effects assembled below (sections III and IV) are based mainly on the records of the women who did not conceive and were therefore transferred to the second trial; in those that became pregnant the first few cycles before the established occurrence of conception have also been included in the analysis.

Acceptability of Method and Compliance with Instructions

Acceptability.—Taking the group as a whole, the method proved highly acceptable. Many of the women had joined the trial because of their professed dissatisfaction with more conventional techniques; throughout the trial they continued to express their preference for the tablets, in spite of experiencing various and occasionally disagreeable side-effects, and, more remarkable still, after it had become clear that the method was not infallible. Several stated spontaneously that they felt "well" or better than they had before beginning to take the tablets. Most of them seemed to tolerate the compound without undue difficulty and none felt compelled to withdraw from the trial because of side-effects, although two did so for that reason after having changed over to the 5-mg. tablets.

Compliance with Instructions.—So far as can be ascertained, the instructions were most conscientiously observed by all volunteers, especially those concerning the daily taking of tablets, recording this and the other required details on the diary cards, and applying for fresh supplies of norethynodrel when necessary. All cards were regularly and rigorously scrutinized, both when returned to the clinic and repeatedly during the survey on which this report is based. Except in cases of breakthrough bleeding, there were no more than six occasions on which tablets were missed. In all but one of them the deficiency amounted to only a single tablet, and was compensated by taking two tablets the next day in accordance with instructions. Such minor deviations have been ignored. The one exception was the omission of three consecutive tablets in one cycle, but this was followed by a normal menstrual period. Apart from these few isolated cases we are satisfied that the tablets were taken in the manner and numbers prescribed, and that failure by the volunteers to do so was not responsible for the observed low efficacy of the compound.

Group Comparisons

All the more important details about the participants of the survey are listed in Table II. It shows that they were divided into two main sections, according to the interval between successive courses of medication. This was first set at eight days, but in the case of later entrants to the trial it was set at six days (cf. Fig. 1). Once allotted to a given division, each woman remained in it throughout the trial, and the second one (2 OC) as well.

TABLE II.—*Group Comparisons*

	All Subjects	Non-pregnant		Pregnant	
		8-day	6-day	8-day	6-day
No. of cases	48	12	22	6	8
Mean age (years)	29·0	30·4	28·0	30·2	28·8
Mean weight (pre-trial)	9 st. 3·8 lb.	9 st. 1·2 lb.	9 st. 4·6 lb.	9 st. 7 lb.	9 st. 3 lb.
Previous children	2·5	2·6	2·1	3·3	2·5
Previous miscarriages	0·4	0·3	0·3	1·0	0·5
Average duration of course* (days)	27·9	28·5	29·3	25·5	25·7
Average No. of tablets per course	19·1	19·2	19·2	18·5	19·2
Average No. of courses per woman	2·69	3·67	2·09	3·00	2·63
Frequency of intercourse†	22·4%	20·4%	22·5%	21·3%‡	27·5%

* Defined as not fewer than 12 consecutive tablets. † For basis of calculation see text. ‡ Based on five women only (see text).

Since pregnancies occurred in both divisions, each volunteer fell into one of four groups. Table II lists for comparison the principal characteristics of these four groups and of the series as a whole. Apart from the fact that the first women to be enlisted were a little older than later recruits, no major differences are shown between the groups in any relevant respect.

Owing to the marked variation in cycle length (see section III), the frequency of coitus has been expressed as a percentage of the total days in the trial. This definition permits comparison with the results of other studies in which frequency of intercourse is expressed per month—for example, Pincus *et al.* (1960)—or is related to an arbitrary cycle of 28 days. On this basis, for instance, a rate of 25% would represent an average frequency of seven times per month, or approximately twice a week. This figure agrees well with those reported by Pincus *et al.* (1960). In one case of our series the frequency of coitus was unusually high: as it would have unduly affected the mean of the group concerned, the smallest of all, it has been excluded (see

footnote to Table II); it was also excluded from the mean frequency for the series as a whole.

Because of the occurrence of breakthrough bleeding (see section III), the courses of medication showed considerable variation in length. In 80% of all courses, 16 or more tablets were taken, and in 10% 10 or fewer. For convenience the figure of 12 or more tablets has been taken as constituting a *course*. The average duration of a course has been obtained by relating the days in the trial to the number of tablet-courses of 12 or more. These are the conventions used in Table II. It shows that there were no important differences in the length of courses so defined between the various groups of subjects; in the smallest one, however, it averaged 18.5 tablets compared with 19.2 in the rest.

II. Pregnancies

The most important, if unlooked-for, result of the trial was the occurrence of pregnancy in nearly one-third of the participants. Eleven of these resulted in 12 healthy liveborn infants, including one pair of twins. Of the three remaining pregnancies, two ended in miscarriage, while in the third this diagnosis is highly probable but could not be established with absolute certainty (Table III). In at least four and possibly six instances fertilization appears to have taken place during the first course of medication.

TABLE III.—*Conception Related to Tablet Failure*

Tablet Failure*	No.	Pregnant and Delivered	Miscarried
Definite	11	9	2
Probable	2	1	1†
Doubtful	1	1	—
Total ..	14	11	3

* See section II.
† Diagnosis of miscarriage not established with absolute certainty.

We have classified the conceptions into three grades: *definite*, where we are satisfied that pregnancy was undoubtedly due to tablet failure; *probable*, where there was some slight element of doubt, but the balance of evidence was markedly towards a tablet failure; and *doubtful*, where the evidence, though suggestive of failure, was equivocal. Each case has been reviewed in the light of all the information available, which includes details from the patient of tablet-taking, bleeding, and dates of intercourse; dates and results of pregnancy tests; period of gestation and probable time of conception, calculated from birth date; birth weight; and signs of prematurity or postmaturity.

Of the 14 conceptions, 11 were graded as *definite* tablet failure, two as *probable*, and one as *doubtful* (see Table III). If this last case is omitted from the survey the number of conceptions believed to be due to failure of the compound becomes 13 out of 48, or 27%. In a further woman subjected to hysterectomy (for prolapse) after four courses of tablets, a large ripe corpus luteum was observed in one ovary at operation, thereby increasing the proportion of cases showing no inhibition of ovulation to 14 or almost 29%. It may be added that in the single case of twins born during this series the babies were of the fraternal binovular type.

The pregnancy rate has also been related to days in the trial, and thence to a basis of 100 woman-years. It is thus exactly comparable to other published rates given in this form (see, for example, Tietze, 1960). Excluding the one doubtful case, the rate is 130 conceptions for 100 woman-years. Expressed in terms of the average course of tablets (27.9 days; see Table II), it is equivalent to a conception rate of 10%.

Condition of the Newborn

In view of the unusual, and possibly unique, character of the series, special efforts were made to follow up the 11 cases of pregnancy until parturition and in particular to record the state of the babies at birth. Most of the deliveries were domiciliary ones, and the following summary is based on the observations made by the doctors concerned in reply to a specific questionary.

There were 10 single births and one pair of fraternal twins. All were liveborn after apparently normal pregnancies and have survived; only one, a female, was premature, weighing 5 lb. 6 oz. (2,440 g.) and being born after a gestation of 36 weeks.

Of the 12 babies born, 6 were males (including the twins) and 6 females—approximately the expected sex ratio. In none of the females were there any signs of malformation or virilization of the external genitalia or other noticeable abnormalities. The more important data collected about the pregnancies and state of the babies at birth are shown in Table IV.

TABLE IV.—*Details of Deliveries and Babies*

Serial No.	Sex	Weight lb. oz.	Weight g.	Gestation (Weeks)	Delivery	Genitalia	Remarks
3	F	7 14	3,570	42	Spontaneous	N.A.D.	"A little postmature"
4	F	5 6	2,440	36	,,	,,	Previous history of 5 premature babies
8		Miscarriage		10	—	—	
15	F	6 11	3,035	38½		N.A.D.	Slight jaundice
17	F	7 13	3,545	42	Surgical induction		No evidence of postmaturity
19	F	6 12	3,060	38	Spontaneous	,,	
22	M	6 3	2,805	40	,,	,,	Assisted breech delivery
23		Miscarriage*		10	—	—	
24	M	8 8	3,855	40½		N.A.D.	
25	M	9 0	4,081	41½	Spontaneous	,,	
33	F	7 4	3,290	41	,,	,,	
34	M	7 0	3,175	40			
37	{M	6 5	2,865}	39½	,,	,,	
	{M	7 4	3,290}				
46		Miscarriage		9	—	—	

* Diagnosis not fully established.

Neither delivery nor lactation appears to have been affected by medication during pregnancy. This was, of course, restricted to a period of, at most, two months around the time of conception and involved only very small doses of norethynodrel. Even so, the apparent complete lack of adverse effects on either mothers or babies concerned should be stressed especially because of the various reports of such effects following exposure to oral contraceptives that have appeared in recent years (Wilkins *et al.*, 1958; Grumbach *et al.*, 1959; Wilkins, 1960).

III. Menstrual Cycle

Cycle Length

Table V shows the distribution of cycle length. This has been obtained according to the conventional definition, counting from the first day of bleeding up to and including the day before the start of the next period. "Spotting" was recorded by 18 of the 48 women (37.5%) in the series. It occurred on a single

occasion in 15 of them and twice in the rest. It has been ignored in the computation of cycle length. None of our volunteers had got beyond four cycles before the trial was closed.

TABLE V.—*Distribution of Cycle Length*

Days	Cycle				Before Entering Trial	
	1st	2nd	3rd	4th	Stated	Actual*
<20	(14)	(17; 17; 19)	(14)			(19)
20	1	1		1		
21		1	1			
22	2			1		
23	1		2	1		2
24	3	2			1	3
25	1	2			2	5
26	5	2	2		11	7
27	2	1		1	6	9
28		3	2		20	4
29	1	4			1	6
30	2		2		6	1
31	2	1	1		1	4
32	5			1		1
33	2	1				1
34	1		1	1		1
35	1					
>35	(37; 40; 42; 44; 44; 44; 47; 49; 49; 52; 55; 60; 67)	(36; 37; 38; 40; 45; 46; 51)	(39; 42; 55)	(38)		(40; 43)
Total	43	28	15	7	48	47
Mean	33·9	29·6	30·0	28·0	27·5	27·9
Median	32	28	28	27	28	27
>35 days	31%	25%	20%	14%	0	4%

* Duration of cycle immediately preceding entry into trial. (For one patient this figure was not recorded.)
The figures in parentheses are the actual cycle durations when either <20 or >35.

The most noticeable effect has been a lengthening of the cycle. More than a quarter of all cycles observed during medication were of more than 35 days' duration, and over half of our volunteers had at least one cycle exceeding 35 days. As can be seen, the proportion of these prolonged cycles consistently diminished with time. The incidence of short cycles (<20 days) was relatively low (5.3%) (see Table V).

As a better measure of average in a distribution which is clearly very skew, the median has been given in addition to the mean. It represents the middle in rank, as many being below as above that figure. Both median and mean show a progressive diminution with time consistent with the reduction in the number of prolonged cycles.

Participants in the trial were asked at the original medical examination to state their normal menstrual pattern and the date of their last period. They entered the trial on the fifth day of their next menstrual period, details of which were to be recorded on their diary cards. From this information the last two columns of Table V have been compiled, showing the distribution of "stated" and "actual" cycles. A very much wider variation is apparent in the actual compared with the stated, and there is also some evidence for preferences of certain numbers (26, 28, 30) in the latter group.

Duration of Period

Table VI, laid out in a similar form to Table V, shows the distribution of the length of the period after each of the cycles on the tablet, as well as the stated and actual pre-trial lengths. Oddly, the last two columns show the reverse effect to that shown in Table V, for the variation is greater in the stated group than in the actual. The periods following the first and second (tablet) cycles both show increased variability, which diminishes in the succeeding two periods. Although this pattern fits in with the experience of other observers, the reduction in variability in our series may be a consequence of the small number of women who experienced as many as four cycles.

TABLE VI.—*Duration of Period*

Days	Cycle				Before Entering Trial	
	1st	2nd	3rd	4th	Stated	Actual*
2	2	3	1		1	
3		1	2	1	8	1
4	12	5	1	1	3	11
5	17	13	10	4	21	25
6	7	3	1	1	8	9
7	3	2			6	
8	2					1
9		1			1	
Total ..	43	28	15	7	48	47
Mean ..	5·02	4·82	4·53	4·71	5·04	4·98
Median	5	5	5	5	5	5

* Duration of period immediately preceding entry into trial. (For one patient this figure was not recorded.)

Breakthrough Bleeding

Nearly one-third of the tablet courses were cut short by breakthrough bleeding (defined as any interruption before the completion of a course of 20 tablets). Breakthrough was least frequent in the first course of medication, and when it occurred was relatively late—on average on the 21st day of the cycle, at which time there remained only three more tablets to be taken. In subsequent courses the interruption was earlier and was probably the result of ovulation delayed from the preceding cycle (see also Discussion).

When transferring to the second trial after the close of the first, each volunteer had to await the onset of a menstrual period before starting on the double-strength tablets. During the changeover the intermenstrual interval was often prolonged, as observed in other trials (see Searle and Co., 1961a).

IV. Side-effects

In the trial as a whole, side-effects were relatively infrequent and slight. Observations on their occurrence and on changes in weight during the trial are based on 34 subjects who were eventually transferred to the 2 OC trial and five others who contributed experience during one or two cycles before conceiving (cf. section I).

Of this total, 27 subjects (69%) experienced so few, infrequent, and trivial symptoms as to remain virtually free of them (classified as "none or very slight"). In a further seven (18%) side-effects were present but were moderate in character and usually confined to the first or second course of medication, improving or disappearing afterwards ("slight or moderate").

Only five women (12%) recorded more persistent or severe and usually multiple symptoms ("marked"), but, even so, found them tolerable and none withdrew from the trial on their account; two, however, did so after the changeover to 5-mg. tablets.

Because of their highly variable distribution it has been impossible to express individual symptoms on a percentage basis or relate them to the sequence of courses of medication experienced by the group as a whole. Much the most common complaints were headache, often but not invariably accompanied by nausea and sickness and swollen, tender breasts. Between them these accounted, in roughly equal proportions, for some 62% of all symptoms recorded by the subjects. Another important group was backache and abdominal or pelvic pain, at times described as cramp, but distinct from uterine pain ("dysmenorrhoea"). This, too, was

common (about 19%) but generally slight, although in one instance it was intense enough to cause the subject concerned to faint. The only other effects recorded were vaginal discharge (not previously present) and dizziness, either alone or associated with nausea and vomiting. With the progress of the trial there was a tendency for symptoms to become less severe or to disappear.

Changes in Weight.—In addition, volunteers frequently experienced some changes in weight. In one-half of the subjects this amounted to minor fluctuations not exceeding 3 lb. (1,360 g.). In 12 (32%) there was a rise averaging 5 lb. (2.270 g.), and in 7 (18%) a similar fall. In some instances the gain, though considerable, was temporary, and was later followed by a corresponding loss and return towards the pre-trial weight. There appeared to be no consistent or marked correlation between changes in weight and other side-effects of the type referred to above.

Effect of Changeover to 2 OC Trial.—As a rule, transfer to the 5-mg. dosage caused pre-existing symptoms to be intensified or, in subjects previously unaffected, to appear for the first time. In two instances this was sufficient to induce withdrawal from the trial. In most of the remainder, however, the condition improved gradually, and few subjects who continued on trial 2 OC as prescribed for more than a few months appear to have experienced troublesome side-effects. Many of them, in fact, have spontaneously recorded their well-being and improvement in general condition as the result of the medication. Changes in weight, even if considerable earlier on, also tended to become less as the second trial proceeded.

Discussion

Fertility Control

The reported findings leave no doubt that the tablets used in this trial did not provide adequate protection against conception. The proportion of pregnancies that occurred—14 out of 48 or approximately 29%—is much higher than that observed with conventional methods of birth control. If the survey is restricted to "undoubted tablet failures" (see above) the figures are almost unchanged (27%). Expressed differently, they imply a ratio of about 130 conceptions per 100 woman- (or exposure-) years (Pearl, 1939; Stix and Notestein, 1940; cf. Tietze, 1960). This compares with an overall pregnancy rate of 2.7 per 100 exposure-years during medication with 10-mg. tablets of norethynodrel in some 500 Puerto Rican volunteers (Pincus *et al.*, 1960), and is as high as that in completely unprotected subjects. Thus the pregnancy rate in white women not practising contraception is of the order of 80 (60–100) per 100 exposure-years (Tietze, 1960); it was about 200 in a group of Puerto Rican women either before or after withdrawal from the trial (Pincus *et al.*, 1960; Searle and Co., 1961a).

Taken at their face value these findings seem to conflict sharply with the increasing body of opinion indicating that a 2.5-mg. strength of norethynodrel provides conception control sufficient in itself and comparable to that of the 5-mg. and 10-mg. tablets (Pincus, 1960a; Pincus *et al.*, 1960; Medical Advisory Council Family Planning Association, 1960; Napp, 1960; Searle and Co., 1961a; Mears, 1961).

It may be that we were dealing with a group of women of quite exceptional fertility. They were, however, drawn from basically the same population as that which normally attends the Birmingham Family Planning Clinic and previously achieved a similar measure of protection with standard methods such as diaphragms and jellies. The further fact that none of the women who were successfully transferred from the first to the second trial and continued on it have conceived also suggests that they were not exceptionally fertile. The possibility that only the women affected, rather than the rest of the group, failed to take the tablets satisfactorily has already been considered and discounted (see section I).

A much more likely explanation of the ineffectiveness of the tablets is their low content of oestrogen. This, as stated, was 0.036 mg. of EO-3-ME per 2.5-mg. tablet, or approximately 1.4%.

A relatively low oestrogen/progestin ratio had been agreed on in consultation with the manufacturers supplying the tablet, in a deliberate attempt to reduce the incidence of side-effects, such as nausea and other gastro-intestinal symptoms, which are commonly ascribed to the oestrogenic moiety of the compound. This proved to be unjustified. Although the incidence and severity of side-effects in our trial were somewhat lower than reported elsewhere (Pincus *et al.*, 1960; Tyler, 1960; Searle and Co., 1961c), they were accompanied by considerable derangement of the menstrual cycle (such as prolonged amenorrhoea; see section III) and further offset by the almost complete failure to prevent ovulation.

It is well established that oestrogens by themselves can reduce the amount of gonadotrophin released by the anterior pituitary and thereby interfere with ovulation (Dodds, 1961). Their exact role as ovulation inhibitors in oestrogen-progestin mixtures like norethynodrel ("enavid") is not clear, but it is generally agreed that they contribute to, even if they are not wholly responsible for, the antiovulatory effect (Tyler, 1961).

Effective conception control coupled with relative stability of the endometrium appears, however, to require a minimal complement of oestrogen of the order of about 0.075 mg. and preferably 0.1 mg., irrespective of the total progestin content; the amount of EO-3-ME in the tablets used at Birmingham was 0.036 mg. and was presumably below the critical value. Perhaps the most important result of the present study—in spite of its unexpected and disappointing clinical aspects—is that it provides new information clearly supporting such a conclusion. This appears to be consistent with the views of other workers, such as Tyler (1961) and Mears (1961); it is also shared by the manufacturers themselves (Searle and Co., 1961b). It would be of considerable theoretical interest to study the ability of pure or more nearly pure preparations of norethynodrel to suppress ovulation and control menstrual cyclicity.

In certain circumstances even as low an amount of oestrogen as that in the Birmingham trial may provide adequate fertility control. This was reported by Pincus (1960b) in a small group of Puerto Rican women taking 2.5-mg. tablets of norethynodrel containing only 0.0375 mg. (1.5%) and 0.05 mg. (2%) of EO-3-ME. All of them had, however, previously used, and had been controlled by, higher dosages of 5 and 10 mg., with correspondingly greater oestrogen contents.

Again, the above considerations do not necessarily apply to other racial groups, in particular subjects of much lower average body weight, such as Japanese and

Indian women. Information on this aspect is almost completely lacking, but would be well worth while collecting.

It must therefore be concluded that the oestrogen content of the compound used in the present trial was too low—either in absolute amount or in relative proportion to norethynodrel—and thus responsible for the inadequate contraceptive efficacy of the tablets.

Effects on the Cycle

It had been anticipated that the low dosage of norethynodrel employed would result in a high incidence of premature or breakthrough bleeding. This was, in fact, not observed, and a significant feature of the trial was the prolongation of cycles induced by the compound.

Compared with an average of 27.9 days (median 27 days) during the last pre-trial cycle, the mean length during the first cycle under medication was 33.9 days (median 32), and of the total of 43 cycles recorded 13 (31%) lasted for more than 35 days, with maxima of 60 and 67 days (see Table V). Although the number, both absolute and relative, of such prolonged periods progressively diminished with time, the tendency towards a lengthening of the cycle during the trial cannot be questioned.

The reasons for the occurrence of this phenomenon, which was first observed during the trials with 10-mg. tablets, are not clear (cf. Pincus *et al.*, 1960). In the case of very low doses of norethynodrel, as used in the present trial, the most likely explanation is that the compound did not suppress but merely delayed ovulation from one to the subsequent cycle, to be followed either by premature bleeding or, in the event of coitus, by conception. This suggestion cannot be substantiated, since no tests to establish the occurrence of ovulation were carried out; but it is supported, in the cases of pregnancy, by retrospective analysis of birth dates and relating them to the recorded data of sexual intercourse. It is also the explanation advanced in the account by Mears (1961).

On the other hand, the incidence of short cycles, or what is commonly referred to as breakthrough bleeding, was unexpectedly low, cycles of less than 20 days' duration totalling only five. Since isolated episodes of slight bleeding or "spotting" were not considered when computing cycle length, this figure may not be comparable with those reported in other trials and which appear to range from 20 to 30% for women using either 5 or 2.5 mg. of norethynodrel (Tyler, 1960; Napp, 1960; see Searle and Co., 1961c).

Side-effects

Side-effects were generally slight and tolerable, and in this respect the original aim of the trial was realized.

The average number of cycles experienced by individual subjects was, however, small and the findings, though suggestive, do not permit any ultimate conclusions. It was also noticeable that in a large proportion of volunteers the changeover from the 2.5-mg. to 5-mg. tablet tended to accentuate existing symptoms or to bring them on in women who had been free of them on the lower dosage. This tendency was most pronounced soon after the changeover—when two volunteers felt unable to continue and withdrew—but diminished with the progress of the second trial. A similar initial intensification of side-effects appears to have been observed in other surveys in which the reverse change, from a higher to a lower dose—for example, 10 mg. to 5 mg.—of norethynodrel was made (Tyler, 1960; cf. Searle and Co., 1961c).

Summary

A trial has been carried out to test the acceptability and contraceptive efficacy of norethynodrel in a carefully selected and supervised group of women of proved fertility.

With the view to reducing side-effects as well as cost, a low dose of norethynodrel was chosen. The tablets actually used in the trial contained 2.3 mg. with 0.036 mg. of oestrogen (ethinyloestradiol-3-methyl ether).

The tablets were generally acceptable, but, although taken in strict conformity with instructions, failed to control fertility.

Of 48 subjects enrolled, 14 (29%) conceived, resulting in 11 pregnancies and three miscarriages. Ten single babies and one pair of twins have been born; all were healthy and there were no signs of virilization of females or other noticeable abnormalities among them.

The remaining 34 volunteers who had not conceived before the trial was closed were changed over to tablets containing 5 mg. of norethynodrel and 0.075 mg. of oestrogen. No pregnancies have occurred in the women who continued to take this dosage as instructed.

During the trial side-effects such as headache, nausea, tender breasts, and abdominal pain were relatively frequent but were usually slight and tended to diminish with time; the same was true of changes in weight. No participants withdrew because of these effects.

The tablets, however, caused derangement of the cycle, as a rule towards prolongation, short cycles (or breakthrough bleeding) being unexpectedly rare.

The results obtained are compared with those of similar trials reported in the literature.

It is suggested that with doses of norethynodrel as low as 2.5 mg. the concentration of oestrogen becomes critical and, if below it, may reduce or abolish the contraceptive activity of the compound, probably by delaying ovulation rather than completely inhibiting it.

We wish to pay tribute to the former chairman, now president, of the Birmingham Family Planning Association, Mrs. Lella Florence, whose interest and enthusiasm were responsible for the inception of the trial; and, equally, to her successor, Mrs. A. K. Court, and her colleagues, Mrs. M. A. MacMillan and Mrs. E. V. Hill, on the staff of the clinic, without whose steady and capable support it could not have been conducted. We also acknowledge our indebtedness to Messrs. G. D. Searle and Co. Ltd., High Wycombe, Bucks, and their medical director, Dr. G. R. Venning, both for the supply of the tablets of norethynodrel and for substantial financial help and advice during the progress of the trial. Finally we wish to thank all those anonymous volunteers who by agreeing to participate in the trial and by their conscientious record-keeping made the whole investigation possible.

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CLINICAL TRIALS OF ORAL CONTRACEPTIVES*

BY

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It has been known for some years that the steroids existing in nature could inhibit ovulation in woman. Practically, however, these steroids were not of value as anti-fertility agents, because of either the undesirable side-effects produced or the lack of therapeutic effectiveness on continued therapy. For example, testosterone produces undesirable androgenic effects; progesterone requires very large doses and its action is too variable; and oestrogens, although they will inhibit ovulation in some cycles, are claimed by some workers not to do so in every cycle (Drill, 1959); while long-term administration of oestrogen is complicated by irregular menstrual bleeding, which may be heavy.

Pincus and his colleagues in 1955 first found that some newer orally active steroids, mostly 19-nor compounds, would inhibit ovulation in the rat and the rabbit. This finding initiated extensive endocrinological and clinical testing of these compounds. Over 200 new steroids have been tested, but the two which have been most used are norethisterone and norethynodrel. Norethynodrel, which has been subjected to most intensive study by Pincus and his colleagues, appeared to be particularly interesting, as it was the first steroid to possess both progestational and oestrogenic activity in the same molecule.

These early trials showed that 10 mg. of norethynodrel ("enavid") plus 0.15 mg. of ethinyloestradiol-3-methyl ether (EO-3-ME) taken for 20 days from day 5 of the cycle was an effective contraceptive, and there was no indication of escape from contraceptive effect with time. Side-effects which occurred in a significant proportion of subjects—particularly vomiting, nausea, dizziness, headache—were found to be more frequent in the first cycle of medication and to decrease thereafter. The addition of oestrogen to the progestogen itself was found to be necessary to maintain the endometrium and prevent spotting and breakthrough bleeding, though this still occurred despite regular taking of tablets. On the whole, patients had regular bleeding and a decreased menstrual flow. Of Pincus's volunteers, 20% gave up in the first year, largely because of these side-effects, while among Tyler's more sophisticated women in Los Angeles 474 out of 715 (66%) discontinued.

As the side-effects and high cost were a disadvantage, 5-mg. tablets containing 0.075 mg. of EO-3-ME were tried and found to be equally effective, and later 2.5 mg. had been used with varying amounts of oestrogen and with apparently similar results.

These early trials were watched in this and other countries with interest and caution: would there be any harmful effects from pituitary inhibition, any possible carcinogenic effect from the administration of steroids; would fertility be restored when the tablets were discontinued? By 1959 it seemed that these anxieties were unjustified, and preliminary carefully controlled clinical trials were instituted under the auspices of the Council for the Investigation of Fertility Control (chiefly undertaken by Dr G. I. M. Swyer and Dr. Margaret Jackson) of some of the available oral progesterones. In 1960 the Medical Advisory Council gave careful consideration to the question of the advisability of using the progestational steroid norethynodrel plus oestrogen as a contraceptive under the conditions planned for clinical trials and was satisfied that it would be safe to use in the way planned. At that time the total experience of norethynodrel included over 20,000 cycles of administration in over 1,000 women, including 150 who had received norethynodrel from 12 to 21 consecutive cycles and 66 women who had taken it from 24 to 38 consecutive cycles.

Large-scale clinical trials were then initiated, the first in Birmingham, followed soon after by another in Slough, and a third has recently begun at the Family Planning Association Headquarters in London.

Thus it will be seen that the trials initiated by the Council are of two distinct kinds: first, small, carefully controlled preliminary trials of a more scientific nature, and later large-scale clinical trials.

Preliminary Trials

Before any of these substances are used in clinical trials on women, careful consideration is, of course, given to the data available from the manufacturers, including particularly the animal screening tests for acute and chronic toxicity, and for androgenic, progestogenic, and oestrogenic properties. When it is felt that enough is known at this level, the substances are used in a number of tests which have been devised for preliminary screening in women.

These tests are usually undertaken with the pure progestogen and with the progestogen with added oestrogen.

1. *An assessment of the ability to postpone menstruation in women with regular cycles.*—An appropriate dose such as 5 mg. is administered daily from the twentieth day of the cycle for 20 days. If menstruation occurs before the 20 tablets have been taken, the result is negative and the test is repeated in the following cycle with double the dose. If menstruation does not occur until after completing the course, the result is positive and the test is repeated with

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